Tumor Variants by Hormone Receptor Expression in White Patients With Node-Negative Breast Cancer From the Surveillance, Epidemiology, and End Results Database

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Purpose: **Hormone receptor expression (presence-positive or absence-negative) may reflect different stages of one disease or different breast cancer types. Determining whether hormone receptor expression represents one or more breast cancer phenotypes would have important paradigmatic and practical implications.**

Methods: **Breast cancer records were obtained from the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) database. The study included 19,541 non-Hispanic white women with node-negative breast cancer. Standard tumor cell characteristics and breast cancer-specific survival were analyzed by independent estrogen receptor (ER+ and ER−), independent progesterone receptor (PR+ and PR−), and joint ERPR expression (ER+PR+, ER+PR−, ER−PR+, and ER−PR−).**

Results: **Age frequency density plots by hormone receptor expression showed two overlapping breast cancer populations with early-onset and/or late-onset etiologies. Independent ER+ and PR+ phenotype were associated with smaller tumor sizes, better grade, and better cancer-specific survival than ER− and PR− breast cancer types. Joint ERPR phenotype exhibited biologic gradients for tumor size, grade, and cancer-specific survival, which ranked from good to worse for ER+PR+ to ER+PR− to ER−PR+ to ER−PR−.**

Conclusion: **Variations of standard tumor cell characteristics and breast cancer–specific survival by hormone receptor expression in white patients with node-negative breast cancer suggested two breast cancer phenotypes with overlapping etiologies and distinct clinical features.**

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CONVENTIONAL WISDOM views breast cancer as a multistep process with a spectrum of proclivities (or stages); that is, one disease along a linear biologic pathway from early to late tumor stages.[1-5] Albeit the etiologic mechanisms of breast carcinogenesis are not fully understood, decades of research suggest an important role for the reproductive hormones (especially estrogen) and their nuclear receptors.[6-10] Presumably, the carcinogenic insult initiates genomic alterations in estrogen-sensitive breast epithelium (estrogen receptor–positive, or ER+), and this insult is promoted by estrogen. ER+ tumor cells then drift to estrogen insensitive (ER−) tumor cells.[11] In this model, ER+ to ER− phenotypic drift is a product of clonal evolution and expansion, reflecting different tumor stages rather than different breast cancer types.[12]

However, ER expression may be a stable phenotype.[13] Sequential ER assays generally do not show ER+ to ER− phenotypic drift from primary to metastatic breast carcinoma.[14] Additionally, if tumor cells did drift from ER+ to ER−, it is counterintuitive for ER+ breast cancer to increase with patient aging.[15,16] Taken to its logical conclusion, the spectrum model predicts that younger (not older) women should have ER+ disease. Absent ER+ to ER− phenotypic drift would suggest that variations in hormone receptor expression represent different breast cancer types rather than different tumor stages.[17-20] Establishing whether hormone receptor expression represents one or more breast cancer types (or variants) has important paradigmatic and practical implications.[5,21-26]

To investigate putative breast cancer variants, we examined patient age at diagnosis, tumor size, histologic grade, and breast cancer survival by independent ER, independent progesterone receptor (PR), and joint ERPR phenotype. Results suggested that hormone receptor phenotype reflects two types of breast cancer with early-onset and/or late-onset variants.

METHODS

Breast cancer records were obtained from the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) Cancer Incidence Public-Use CD-ROM, 1973 through 1996, August 1998 submission. The original breast.txt raw data file was imported from the Public-Use CD-ROM to SAS for Windows (Version 6.12, SAS Institute, Cary, NC), S-Plus 2000 for Windows (Statistical Sciences, Seattle, WA), and Statistica for Windows '99 edition (Version 5.5A, StatSoft, Tulsa, OK). Collected from nine population-based cancer registries, the SEER database includes 2.3 million cancer cases from representative American subsets comprising 9.5% of the United States population.[27] SEER did not gather hormone receptor data before 1990.

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This analysis was restricted to white women with node-negative breast cancer who were accrued during the years of hormone receptor collection.

From 1990 through 1996, there were 132,159 breast cancer records in the Public-Use CD-ROM. This breast cancer cohort was sequentially filtered for the following: (1) female sex (n = 131,306); (2) infiltrating ductal carcinoma not otherwise specified (histopathologic code 8500; n = 79,768); (3) one or first primary breast cancer only (n = 68,801); (4) microscopic confirmation (n = 68,775); (5) American Joint Committee on Cancer tumor sizes T1-T3[28] corresponding to SEER extent of disease codes 10 through 30 (n = 63,309); (6) axillary lymph node–negative breast cancer cases (n = 40,491); (7) tumor size ≤ 5.0 centimeters (n = 37,871); (8) records with complete information for histologic grade (n = 29,671), ER expression (presence-positive or absence-negative; n = 24,445), and PR expression (presence-positive or absence-negative; n = 23,483); (9) non-Hispanic white race (n = 19,541).

Study variables included standard tumor cell characteristics, patient age at diagnosis, tumor size, histologic grade, and hormone receptor expression. All study variables were stratified by independent ER, independent PR, and joint ERPR expression. Tumor size and age were analyzed as continuous and categoric variables. Age less than 50 years versus 50+ years was a surrogate measure for menopausal status. Tumor size was divided into two groups: more than 2.0 centimeters versus ≤ 2.0 centimeters, corresponding to American Joint Committee on Cancer stage IIA versus stage I. Histopathologic grading and differentiation were defined according to the *International Classification of Diseases for Oncology* (ed 2): grade 1, well differentiated; grade 2, moderately differentiated; grade 3, poorly differentiated; and grade 4, undifferentiated.[29] Because grade 1 and grade 4 comprised less than 20% of the breast cancer records, we collapsed histologic grade into two categories, with grades 1 and 2 being considered a good prognostic group and grades 3 and 4 a poor category. SEER has no standard definition or centralized laboratory to determine hormone receptor expression. Depending on the assay used, each SEER site codes ER and PR expression as presence-positive or absence-negative.

Student's *t* test for independent samples and one-way analysis of variance were used to detect differences in mean ages at diagnosis between groups defined by hormone receptor expression.[30] Continuous 1-year age frequency distributions were generated with density plots, which were constructed with a smoothing method of the corresponding age-at-diagnosis frequency histogram.[31] Using the density function in S-Plus 2000,[32] the density plot used a filter width of 10. The vertical axis for each density plot represented smoothed estimates of the proportion (or density) of patients who developed breast cancer at the corresponding age at diagnosis on the horizontal axis. Kolmogorov-Smirnov statistics tested statistically significant differences between age frequency distributions.[33] Kolmogorov-Smirnov statistics define the maximum difference in the cumulative proportions of two nonparametric distributions. Univariate and multivariate associations between hormone receptor expression and study variables were estimated with odds ratios and *P* values. Logistic regression was used to derive adjusted odds.[34] All *P* values were two-sided. *P* values ≤ .05 were considered statistically significant.

Outcome measures included overall survival and breast cancer–specific survival. SEER's vital status code established whether the patient was alive or dead. Cause of death was categorized as either breast cancer–specific or non–breast cancer death. Overall survival was defined as the interval between date of breast cancer diagnosis and date of death from any cause. Breast cancer–specific survival was measured from the date of diagnosis to the date of breast cancer–specific death. The Kaplan-Meier product-limit method estimated overall and breast cancer–specific survivals from 1990 to 1995.[35] Stratified log-rank test compared time to overall and cancer-specific survivals between groups by independent and/or joint hormone receptor expression.[36]

RESULTS

Descriptive statistics by independent ER and independent PR phenotypes yielded similar results (Tables 1 and 2, respectively). ER− compared with ER+ and PR− compared with PR+ were both associated with younger age at diagnosis, surrogate premenopausal status, larger tumor diameter, and poor histologic grade. Age frequency density plots showed bimodal distribution with early-onset mode (or peak frequency) and/or late-onset mode (or peak frequency; Fig 1). The vertical axis of each density plot represented smoothed estimates of the proportion of patients who had breast cancer at the corresponding age at diagnosis on the horizontal axis. Early-onset peak frequency approximated the premenopausal age of 40 to 50 years, whereas late-onset peak frequency occurred close to the postmenopausal age of 70 years. The postmenopausal peak predominated in ER+, PR+, and PR− phenotypes, whereas the premenopausal peak was dominant with ER− breast cancer.

Descriptive statistics by joint ERPR phenotypes are listed in Tables 3 and 4. A total of 66% (n = 12,811) were ER+PR+, 12.5% (n = 2,436) were ER+PR−, 3.4% (n = 663) were ER−PR+, and 18.6% (n = 3,631) were ER−PR−. Mean age at diagnosis was significantly different ($P < .001$) by one-way analysis of variance for joint ERPR profiles: 62.7 years for ER+PR+, 65.1 years for ER+PR−, 55.2 years for ER−PR+, and 57.0 years for ER−PR−. All possible pairs of mean age were also significantly different by Student's *t* test for independent samples, after adjusting for multiple comparisons. Age frequency distribution density plots by joint ERPR status are shown in Fig 2. The concordant ERPR pair (ER+PR+ and ER−PR−) demonstrated bimodal premenopausal and postmenopausal peaks. The postmenopausal peak dominated in the ER+PR+ phenotype, whereas the premenopausal peak was dominant in ER−PR− expression. The discordant ERPR pair (ER+PR− and ER−PR+) had unimodal age frequency density plots. Frequency distribution was shifted to the right (towards late-onset or postmenopausal ages) for ER+PR−; peak distribution approximated 70 years of age. ER−PR+ was the reciprocal of ER+PR−; that is, peak frequency distribution was shifted to the left (towards early-onset or premenopausal ages) with peak frequency distribution between 40 and 50 years.

To further compare the age frequency distribution curves by independent and joint hormone receptor expression, we examined the Kolmogorov-Smirnov nonparametric test statistics. The largest test statistic was observed when ER+PR− was compared with ER−PR+ (Kolmogorov-

Table 1. Descriptive Statistics by Independent ER Expression

	ER+		ER−		Unadjusted Odds Ratio	P
	No. of Patients	%	No. of Patients	%		
Sample size	15,247		4,294			
Mean age, years	63.1		56.7			< .001
Mean tumor size, cm	1.55		1.83			< .001
Univariate model						
Age at diagnosis						
< 35 years	189	1.2	157	3.7	4.64	< .001
35 to < 50 years	2,728	17.9	1,350	31.4	2.76	< .001
50 to < 65 years	4,718	30.9	1,424	33.2	1.69	< .001
65+ years	7,612	49.9	1,363	31.7	1.00	
Menopause						
< 50 years	2,917	19.1	1,507	35.1	2.29	.001
50+ years	12,330	80.9	2,787	64.9	1.00	
Tumor size						
> 2.0 cm	2,999	19.7	1,401	32.6	1.98	.001
≤ 2.0 cm	12,248	80.3	2,893	67.4	1.00	
Histologic grade						
Poor	4,431	29.1	2,777	64.7	4.47	.001
Good	10,816	70.9	1,517	35.3	1.00	

Multivariate Model	Comparison	Adjusted Odds Ratio*	P
Menopause	< 50 years *v* 50+ years	1.99	< .001
Tumor size	> 2.0 cm *v* ≤ 2.0 cm	1.41	< .001
Histologic grade	Poor *v* good	4.01	< .001

NOTE. The logit estimator compared ER− with ER+.

*Adjusted odds ratio was derived with logistic regression.

Smirnov test statistic of 0.3366). The Kolmogorov-Smirnov test statistic between ER+ and ER− was larger than the test statistic between PR+ and PR− (0.1996 and 0.0601, respectively). All Kolmogorov-Smirnov test statistics were statistically significant ($P < .001$).

Tumor size and histologic grade showed a type of dose response (or biologic gradient) with joint hormone receptor expression, which were ranked from good to worse for ER+PR+ to ER+PR− to ER−PR+ to ER−PR− (Tables 3 and 4). Age at diagnosis and surrogate menopausal status showed no biologic gradient by ERPR phenotype. With multivariate modeling, all relationships remained statistically significant except for tumor size in the ER−PR+ group ($P = .314$) (Table 4).

From 1990 to 1995, the median duration of follow-up was 31 months. Crude unadjusted overall survival was 92.7%. There were 18,114 living and 1,427 deceased patients: 904 non–breast cancer deaths and 523 breast cancer deaths. Kaplan-Meier product-limit analysis demonstrated significant differences (log-rank test, $P < .001$) for both overall and breast cancer–specific survival by independent ER, independent PR, and joint ERPR profiles. Log-rank χ^2 results were greater for cause-specific than for overall survival, demonstrating that hormone receptor expression had a greater impact on breast cancer–specific than overall survival. Kaplan-Meier plots for breast cancer–specific survival by hormone receptor expression are shown in Fig 3. ER+ compared with ER− and PR+ compared with PR− showed improved survival. ER+ and PR+ had identical cancer-specific survival. There was a biologic gradient by joint ERPR phenotypes for cancer-specific survival, with worsening cumulative proportion surviving from ER+PR+ to ER+PR− to ER−PR+ to ER−PR−.

DISCUSSION

Although there is abundant information concerning independent ER and PR expression, comparatively little is known concerning joint ERPR phenotype. In part, this is because there are relatively few ER+PR− tumors and even fewer ER−PR+ cancers. Clark et al[15] and others[37,38] have noted varied hormonal expression by ER and PR phenotype in both early-stage and late-stage breast cancers. To further evaluate the importance of independent as well as joint hormone receptor expression in early-stage breast cancer, we examined the National Cancer Institute's SEER population-based database.

Independent ER+ and independent PR+ expression were associated with older age at diagnosis, smaller tumor sizes,

Table 2. Descriptive Statistics by Independent PR Expression

	PR+		PR−		Unadjusted Odds Ratio	*P*
	No. of Patients	%	No. of Patients	%		
Sample size	13,474		6,067			
Mean age, years	62.3		60.3			< .001
Mean tumor size, cm	1.54		1.77			< .001
Univariate model						
Age at diagnosis						
< 35 years	173	1.3	173	2.9	2.52	< .001
35 to < 50 years	2,678	19.9	1,400	23.1	1.32	< .001
50 to < 65 years	4,199	31.2	1,943	32.0	1.17	< .001
65+ years	6,424	47.7	2,551	42.0	1.00	
Menopause						
< 50 years	2,851	21.2	1,573	25.9	1.30	.001
50+ years	10,623	78.8	4,494	74.1	1.00	
Tumor size						
> 2.0 cm	2,586	19.2	1,814	29.9	1.80	.001
≤ 2.0 cm	10,888	80.8	4,253	70.1	1.00	
Histologic grade						
Poor	3,860	28.6	3,348	55.2	3.07	.001
Good	9,614	71.4	2,719	44.8	1.00	

Multivariate Model	Comparison	Adjusted Odds Ratio*	*P*
Menopause	< 50 years *v* 50+ years	1.12	.004
Tumor size	> 2.0 cm *v* ≤ 2.0 cm	1.41	< .001
Histologic grade	Poor *v* good	2.86	< .001

NOTE. The logit estimator compared PR− with PR+.

*Adjusted odds ratio was derived with logistic regression.

better histologic grade, and better breast cancer–specific survival than ER− and PR− disease. Age frequency density plots showed mixed breast cancer populations, with overlapping early-onset (premenopausal) and late-onset (postmenopausal) breast cancer types. ER+, PR+, and PR− had dominant postmenopausal peaks, whereas ER− had a dominant premenopausal peak (Fig 1). The trough between the bimodal peaks may represent the so-called Clemmesen's hook, the characteristic midlife dip in age-specific breast cancer incidence that is attributed to the female climacteric.[39,40] Purportedly, Clemmesen's hook occurs at the junction of declining premenopausal breast cancer incidence and increasing postmenopausal breast cancer incidence. The midlife drop approximated 58 years of age in this analysis.

It has been suggested that joint ERPR expression identifies breast cancer variants better than either independent ER or PR expression.[18,20,26] There may be general agreement concerning concordant joint profiles (ER+PR+ and ER−PR−), but the discordant pair (ER+PR− and ER−PR+) has been problematic. ER+PR+ represents hormone-responsive breast cancer, whereas ER−PR− reflects hormone-insensitive tumors.[18,41] In contrast, ER+PR− and/or ER−PR+ have been characterized as dubious discordant subsets,[18] mutant pairs,[42,43] laboratory artifacts,[44] and imaginary.[45] However, in this analysis, the discordant joint ERPR phenotypes had distinct age frequency density plots and prognostic factor profiles.

The purest postmenopausal age frequency distribution was in the ER+PR− group, whereas the purest premenopausal pattern had ER−PR+ expression (Fig 2). for ER+PR− expression, the mean age at diagnosis was 65.1 years, with a single peak frequency distribution of 70 years, similar to the age of greatest risk for sporadic breast cancer.[27,46] For ER−PR+ expression, peak age frequency distribution was between 40 and 50 years of age. Consequently, the oldest patients had a joint ER+PR− profile, whereas the youngest women were in the ER−PR+ group, consistent with the association of increased ER concentrations with aging and increased PR concentrations with premenopausal status.[16,17,47-49] Greater premenopausal levels of endogenous estrogens presumably induce PR expression. Therefore, because increasing ER level is associated with increasing age and increasing PR level is associated with premenopausal status, it makes sense for ER+PR− to include the oldest women while ER−PR+ contains the youngest patients. Intermediate mean ages and age frequency distribution patterns are in the concordant

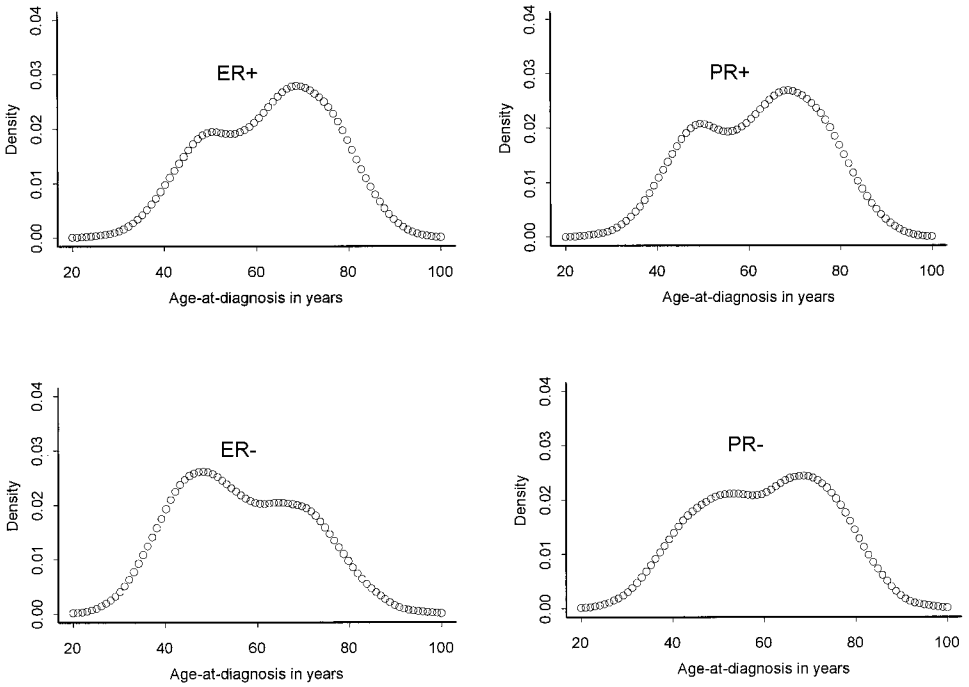

Fig 1. Age frequency density plot by independent ER and PR phenotype.

groups, with ER+PR+ women being older than are ER−PR− women.

There is thus a complicated relationship between age at diagnosis and menopausal status, which is reflected by joint ERPR phenotypes. Menopausal status was a surrogate measure in this analysis, but the Iowa Women's Health Study collected reproductive history as well as other epidemiologic risk factors from a self-reported questionnaire.[26] Sporadic breast cancer was highly associated with ER+PR−, whereas family history of breast cancer had its strongest association with ER−PR+ profile. Similarly, a case-control analysis in Japan reported that family history was not associated with ER+PR− expression.[50] Loman et al[51] also suggested that familial tumors with high levels of PR might compose a distinct subgroup of hereditary breast carcinomas that are not related to *BRCA1* and/or *BRCA2*. All three studies are consistent with our observation for the oldest and youngest patients to be in the ER+PR− and ER−PR+ groups, given that sporadic and familial breast cancers tend to occur in older and younger women, respectively.[27,52,53] The Iowa Women's Health Study described joint ER+PR− expression as true sporadic breast cancers. The ER−PR+ profile could be a familial equivalent. Future etiologic studies should possibly focus on discordant ERPR phenotypes for analyzing sporadic and familial breast cancer.

Tumor size, grade, and breast cancer survival demonstrated biologic gradients, whereas age at diagnosis and menopausal status showed no biologic gradients by joint ERPR expression. Tumor size (> 2.0 *v* ≤ 2.0 cm) and grade (poor *v* good) increased, whereas cancer-specific survival decreased from ER+PR+, ER+PR−, ER−PR+, and ER−PR−. The absence of a biologic gradient for age at diagnosis and/or menopausal status was due to the fact that the oldest and youngest patients were associated with the discordant joint phenotypes (Table 3), which had intermediate cancer-specific survivals (Fig 3).

This analysis has several potential sources of error that could effect internal and/or external validity. First, hormone receptor assays were not carried out in a centralized laboratory. However, ER and PR assays are now obtained on virtually every breast cancer patient and assay technology is becoming standardized.[54] Overall conclusions from a variety of different laboratories using different assays have usually been consistent.[55] It also seems highly unlikely that nine SEER sites would have differential hormone receptor misclassification across the four ERPR phenotypes. We derived some comfort from the fact that our joint ERPR distribution was very similar to other American studies; that is, ER+PR+, ER+PR−, ER−PR+, and ER−PR− are approximately 60%, 15% to 20%, less than 5%, and 15% to 20%, respectively.[18,26,41] In contrast, our hormone receptor distribution is strikingly different from a Japanese case-control study, which noted that ER+PR+, ER+PR−, ER−PR+, and ER−PR− were 39%, 25%, 5%, and 31%,

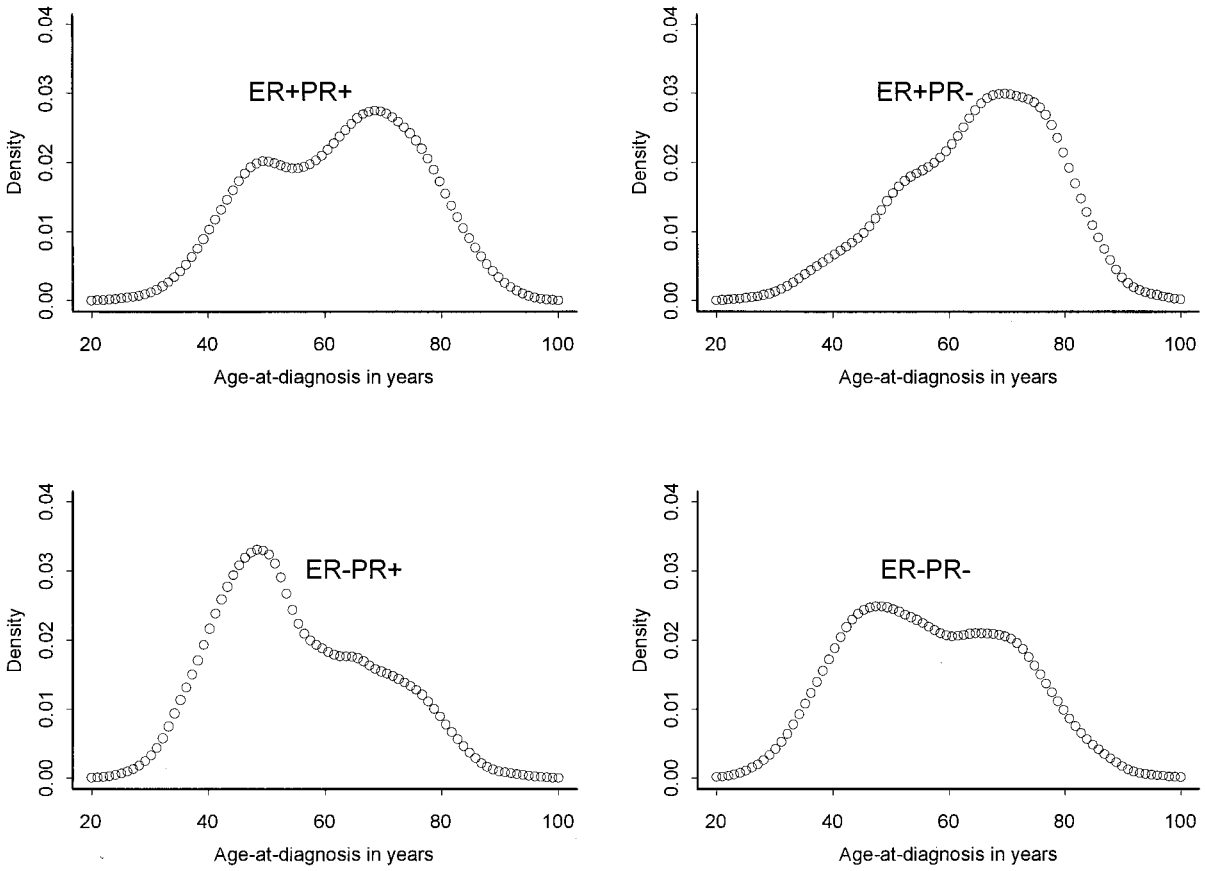

Fig 2. Age frequency density plot by joint ERPR phenotype.

respectively.[50,56] However, joint ERPR distribution by Japanese ethnicity in the SEER database is also different from the Japanese case-control study in Japan. There were 595 Japanese women with lymph node–negative breast cancer in the SEER 1973 through 1996 CD-ROM, and ERPR profiles were 69.6%, 12.1%, 5.2%, and 13.1% for ER+PR+, ER+PR−, ER−PR+, and ER−PR−, respectively. Japanese women in Japan and in America may have different breast cancers, or different ERPR phenotypes could have been due to selection bias, because joint receptor status was unknown in 60% of the Japanese cases in Japan.

Second, our results may not be generalizable to the global breast cancer population, because we examined a lymph node–negative subset from the SEER population-based database containing only non-Hispanic white women with infiltrating ductal carcinoma. We reasoned that early-stage breast cancer in a single ethnic group would reduce late-stage confounding of interrelated study variables such as race, delayed breast cancer detection, socioeconomic status, and so on.[57-65] A preliminary analysis has confirmed racial variation by joint ERPR phenotype especially for black versus white women, but this will be the subject of another report. A future report could also incorporate node-positive breast cancer patients.

A third concern relates to the fact that the SEER Public-Use CD-ROM does not include information pertaining to postoperative adjuvant treatment. Therefore, breast cancer outcome could not be adjusted for postoperative treatment. However, the observed biologic gradient (ER+PR+ to ER+PR− to ER−PR+ to ER−PR−) is not only biologically plausible but also consistent with previous studies. Wenger et al[44] reported in 1993 that S-phase fraction increased from ER+PR+, ER+PR−, ER−PR+, and ER−PR−. S-phase fraction is strongly correlated with poor breast cancer prognosis.[66] Early Breast Cancer Trialists' Collaborative Group also observed relative improvements in early-stage breast cancer survival associated with adjuvant tamoxifen therapy, which were ranked from good to worse for ER+PR+ to ER+PR− to ER−PR+ to ER−PR−.[67] Additionally, hormone receptor status was first noted to be a predictor of cancer-specific

Table 3. Descriptive Statistics by Joint ERPR Expression

	ER+PR+		ER+PR−		ER−PR+		ER−PR−	
	No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%
Mean age, years	62.7		65.1		55.2		57.0	
Mean tumor size, cm	1.54		1.62		1.63		1.87	
Sample size	12,811	65.6	2,436	12.5	663	3.4	3,631	18.6
Age at diagnosis								
< 35 years	156	1.2	33	1.4	17	2.6	140	3.9
35 to < 50 years	2,432	19.0	296	12.2	246	37.1	1,104	30.4
50 to < 65 years	3,975	31.0	743	30.5	224	33.8	1,200	33.0
65+ years	6,248	48.8	1,364	56.0	176	26.5	1,187	32.7
Menopause								
< 50 years	2,588	20.2	329	13.5	263	39.7	1,244	34.3
50+ years	10,223	79.8	2,107	86.5	400	60.3	2,387	65.7
Tumor size								
> 2.0 cm	2,428	19.0	571	23.4	158	23.8	1,243	34.2
≤ 2.0 cm	10,383	81.0	1,865	76.6	505	76.2	2,388	65.8
Histologic grade								
Poor	3,547	27.7	884	36.3	313	47.2	2,464	67.9
Good	9,264	72.3	1,552	63.7	350	52.8	1,167	32.1

survival more than 20 years ago, before routine adjuvant systemic treatment.[16,68] Hormone receptor status is also known to have prognostic value in node-negative patients who did not receive systemic treatment.[69,70]

Fourth, the short median follow-up time of 31 months may not be adequate to detect long-term survival differences in node-negative breast cancer. However, ER studies with short-term follow-up (2 to 4 years) can yield valid conclusions concerning breast cancer etiology and early outcome effects, but late outcome results will require long-term follow-up.[16,71] Therefore, our early survival results must be verified with longer follow-up.

Notwithstanding these theoretical limitations, this is the largest node-negative population-based breast cancer analysis (n = 19,451) to ever simultaneously examine independent ER, independent PR, and joint ERPR expression. Our

Table 4. Univariate and Multivariate Logistic Regression for Study Variables by Joint ERPR Expression

	ER+PR−		ER−PR+		ER−PR−	
	Odds Ratio	*P*	Odds Ratio	*P*	Odds Ratio	*P*
Univariate model						
Age at diagnosis						
< 35 years	0.97	.871	3.87	< .001	4.72	< .001
35 to < 50 years	0.56	< .001	3.59	< .001	2.39	< .001
50 to < 65 years	0.86	.002	2.00	< .001	1.59	< .001
65+ years	1.00		1.00		1.00	
Menopause						
< 50 years	0.62	.001	2.60	.001	2.06	.001
50+ years	1.00		1.00		1.00	
Tumor size						
> 2.0 cm	1.31	.001	1.34	.002	2.23	.001
≤ 2.0 cm	1.00		1.00		1.00	
Histologic grade						
Poor	1.49	.001	2.34	.001	5.52	.001
Good	1.00		1.00		1.00	
Multivariate model						
Menopause, < 50 *v* 50+ years	0.60*	< .001	2.46*	< .001	1.75*	< .001
Tumor size, > 2.0 *v* ≤ 2.0 cm	1.23*	< .001	1.10*	.314	1.57*	< .001
Grade, poor *v* good	1.47*	< .001	2.19*	< .001	4.93*	< .001

NOTE. The logit estimator compared ER+PR−, ER−PR+, and ER−PR− to ER+PR+.

*Adjusted odds ratio (derived with logistic regression).

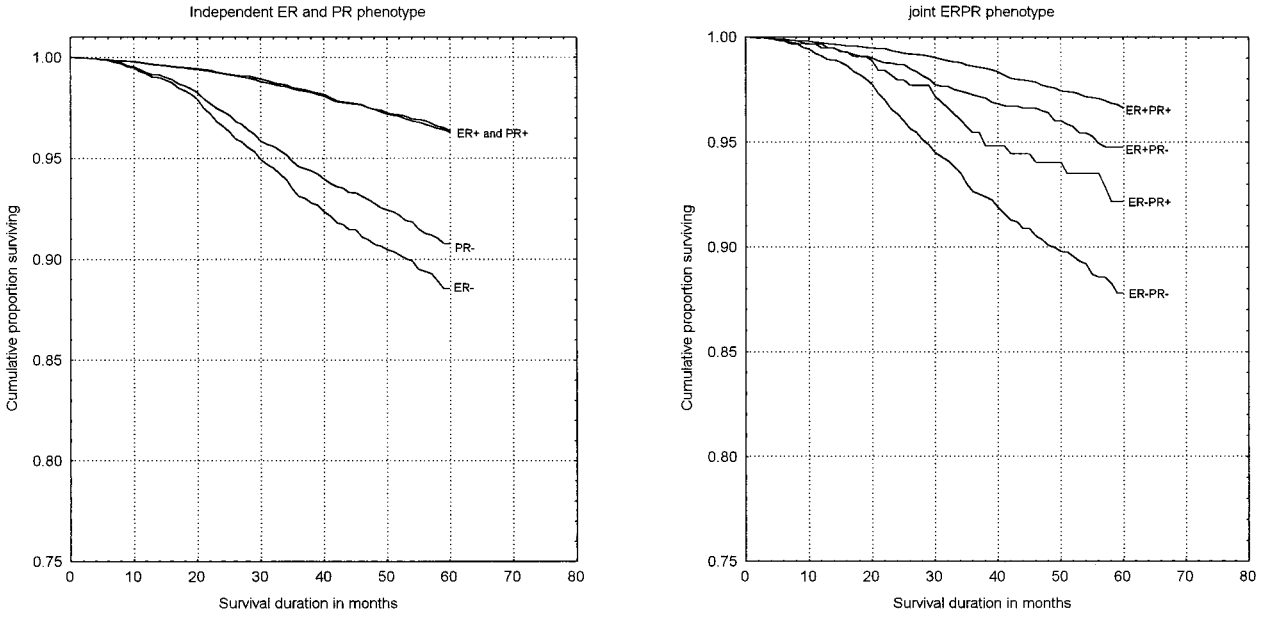

Fig 3. Breast cancer-specific survival by independent and joint hormone receptor expression.

results provide potentially important etiologic clues, clinical insights, and caveats:

1. Although mean age at diagnosis is commonly used to describe breast cancer populations, population means assume normal frequency distributions. Our node-negative white breast cancer cohort had bimodal (not normal) age frequency distribution, and consequently, was also described with density plots. Notably, age frequency density plots by independent ER and PR expression suggested that there were two breast cancer types with overlapping early-onset and late-onset modes (or peak frequencies).

2. The concordant joint ERPR pair (ER+PR+ and ER−PR−) was characterized by a mixture of early-onset (premenopausal) and late-onset (postmenopausal) breast cancer populations. Postmenopausal breast cancer dominated the ER+PR+ phenotype, whereas premenopausal breast cancer was dominant in the ER−PR− phenotype. ER+PR+ and ER−PR− were associated with the best and worst cancer-specific survivals, respectively.

3. The discordant joint ERPR pair (ER+PR− and ER−PR+) had reciprocating unimodal late-onset and early-onset breast cancer variants, which possibly represented pure sporadic and familial breast cancer, respectively. ER+PR− and ER−PR+ had intermediate cancer survivals.

4. ER−PR+ expression seemed to be a true rather than imaginary phenotype or laboratory error.

In conclusion, variations of patient age at diagnosis, tumor size, grade, and cancer-specific survival by independent and joint hormone receptor expression posit two breast cancer variants with overlapping early or late-onset etiologies and distinct clinical features. The contemporary spectrum paradigm postulates that breast cancer is one disease along a continuous biologic pathway.[1-4] Our large-scale population-based observations suggest that breast cancer is two diseases rather than one.

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